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United States Environmental Protection Agency
Office of Pollution Prevention and Toxics

ALLYL ALCOHOL
(CAS Reg. No. 107-18-6)

PROPOSED ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs)

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Oak Ridge National Laboratory, managed by UT-Battelle, LLC, for the U.S. Dept. of Energy under contract DE-AC05-00OR22725

PREFACE

Under the authority of the Federal Advisory Committee Act (FACA) P. L. 92-463 of 1972, the National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances (NAC/AEGL Committee) has been established to identify, review and interpret relevant toxicologic and other scientific data and develop AEGLs for high priority, acutely toxic chemicals.

AEGLs represent threshold exposure limits for the general public and are applicable to emergency exposure periods ranging from 10 minutes to 8 hours. AEGL-2 and AEGL-3 levels, and AEGL-1 levels as appropriate, will be developed for each of five exposure periods (10 and 30 minutes, 1 hour, 4 hours, and 8 hours) and will be distinguished by varying degrees of severity of toxic effects. The NAC/AEGL Committee believes that the recommended exposure levels are applicable to the general population including infants and children who may be sensitive and susceptible. The three AEGLs have been defined as follows:

AEGL-1 is the airborne concentration (expressed as ppm or mg/m^3) of a substance at or above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic, nonsensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.

AEGL-2 is the airborne concentration (expressed as ppm or mg/m^3) of a substance at or above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting adverse health effects, or an impaired ability to escape.

AEGL-3 is the airborne concentration (expressed as ppm or mg/m^3) of a substance at or above which it is predicted that the general population, including susceptible individuals, could experience life-threatening health effects or death.

Airborne concentrations below the AEGL-1 represent exposure levels that could produce mild odor, taste, irritation, or certain subclinical non-sensory effects. With increasing airborne concentrations above each AEGL level, there is a progressive increase in the likelihood of occurrence and the severity of effects described for each corresponding AEGL level. Although the AEGL values represent threshold levels for the general public, including sensitive subpopulations, it is recognized that certain individuals, subject to unique or idiosyncratic responses, could experience the effects described at concentrations below the corresponding AEGL level.

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EXECUTIVE SUMMARY

Allyl alcohol (CAS Reg. No. 107-18-6) is a colorless liquid that is a potent sensory irritant. Toxic effects following inhalation exposures to allyl alcohol vapor include lacrimation, pulmonary edema and congestion, and inflammation, hemorrhage, and degeneration of the liver and kidney. Human data were limited to voluntary exposures for short durations and general statements about the signs of toxicity following accidental exposures to unknown concentrations of allyl alcohol for unspecified amounts of time in the workplace. Animal data were limited to studies in which lethality was the only endpoint of interest, subchronic exposures, or single-exposure experiments in which the model was questionable.

The AEGL-1 value was based on the mean odor detection threshold concentration of 1.8 ppm (AIHA, 1989). Odor is considered a threshold effect; therefore the values were not scaled across time, but rather the threshold value is applied to all times.

The AEGL-2 values were based on a subchronic exposure study in which rats were repeatedly exposed to 40 ppm for 7 hours/day (Dunlap et al., 1958). Irritation was noted to occur during the first few exposures. An uncertainty factor of 3 was applied for species to species extrapolation because there did not appear to be much variation between species: a NOEL for lethality was the same for 3 different species (mice, rats, and rabbits). An uncertainty factor of 3 was also applied for intraspecies extrapolation. Although the traditional approach for uncertainty factors in a case such as this would argue for an uncertainty factor of 10 because of the lack of data addressing interindividual variability, this would result in a composite uncertainty factor of 30. An uncertainty factor of 30 would drive the AEGL-2 values (8 hour AEGL-2 of 1.2 ppm) to a level that would be inconsistent with available data: Dunlap et al. (1958) reported that rats exposed for 7 hr/d, 5 days/wk for 60 exposures to 1, 2, or 5 ppm had no observable adverse effects, while rats exposed to 20 ppm only exhibited decreased body weight gain, and Torkelson et al. (1959) reported that no adverse effects were noted when rats, guinea pigs, rabbits, and dogs were exposed to 2 ppm for 7 hr/d, 5 d/wk for 28 exposures, while exposure of rats, guinea pigs, and rabbits exposed to 7 ppm for 7 hr/d, 5 d/wk for 134 exposures exhibited only reversible liver and kidney damage. Therefore, a total uncertainty factor of 10 was applied to the AEGL-2 value.

The experimentally derived exposure value was then scaled to AEGL time frames using the concentration-time relationship given by the equation $C^n \times t = k$, where C = concentration, t = time, k is a constant, and n generally ranges from 1 to 3.5 (ten Berge, 1986). The value of n was not empirically derived due to the unreliability and inconsistencies of the data; therefore, the default value of $n = 1$ was used for extrapolating from shorter to longer exposure periods and a value of n = 3 was used to extrapolate from longer to shorter exposure periods. The 10-minute value was set equal to the 30-minute value because it was considered too precarious to extrapolate from the exposure duration of 7 hours to 10 minutes.

The AEGL-3 values were based upon a NOEL for lethality in mice, rats, and rabbits of 200 ppm for 1 hour (Union Carbide, 1951). An uncertainty factor of 3 was applied for species to species extrapolation because there did not appear to be much variation across species for lethality. A NOEL for lethality was the same for 3 different species (mice, rats, and rabbits), and this endpoint was used for the AEGL-3 derivation. Additionally, the use of a NOEL for lethality is inherently conservative. An uncertainty factor of 3 was also applied for intraspecies

extrapolation. As discussed in the AEGL-2 derivation section, applying the traditional uncertainty factor of 10 to account for the lack of data addressing interindividual variability would result in a composite uncertainty factor of 30, which would drive the AEGL-3 values to a level that would be inconsistent with available data (1 hour AEGL-3 of 6.7 ppm; see AEGL-2 derivation discussion above). Therefore, a total uncertainty factor of 10 was applied to the AEGL-3 value.

The experimentally derived exposure value was then scaled to AEGL time frames using the concentration-time relationship given by the equation $C^n \times t = k$, where C = concentration, t = time, k is a constant, and n generally ranges from 1 to 3.5 (ten Berge, 1986). Again, the value of n was not empirically derived due to the unreliability and inconsistencies of the data; therefore a default value of n should be used in the temporal scaling of AEGL values across time. If one applies the default value of $n = 1$ for extrapolating from shorter to longer exposure periods and a value of n = 3 to extrapolate from longer to shorter exposure periods, one obtains the following values: 10 minutes: 36 ppm; 30 minute: 25 ppm; 1 hour: 20 ppm; 4 hours: 5.0 ppm; 8 hours: 2.5 ppm. Going with a default value results in AEGL values that are inconsistent with the available data. The AEGL-2 data do not support the hypothesis that n=1 for extrapolation to 4 or 8 hours: when using an n=1 (which assumes a "worse case" scenario) to extrapolate from 1 hour to 4 or 8 hours, one obtains a 4-hour AEGL-3 value of 5.0 ppm, which is almost identical to the 4-hour AEGL-2 value of 4.8 ppm, and an 8-hour AEGL-3 value of 2.5 ppm, which is lower than the 8-hour AEGL-2 value of 3.5 ppm. The AEGL-2 values help to serve as a baseline: they are based on a multiple exposure scenario in which rats exposed for 40 ppm for 7 hrs/d exhibited reversible signs of irritation. It is unreasonable to have AEGL-3 values below the AEGL-2 values. Therefore, in the absence of any further data, an n of 2 was selected as a reasonable compromise between the possible values for n as reported by ten Berge (1986): it is between the most conservative n=1 (which results in unreasonable values) and an n=3, a least conservative value. AEGL-3 values are therefore derived using an n=3 for extrapolation to 10 and 30 minutes and an n=2 for extrapolation to 4 or 8 hours.

The derived AEGL values are listed in the table.

Summary of Proposed AEGL Values for Allyl Alcohol [ppm (mg/m^3)]

Classification	10-minute	30-minutes	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL-1 (Nondisabling)	1.8 (4.4)	1.8 (4.4)	1.8 (4.4)	1.8 (4.4)	1.8 (4.4)	Mean odor detection threshold (AIHA, 1989)
AEGL-2 (Disabling)	9.6 (23)	9.6 (23)	7.7 (19)	4.8 (12)	3.5 (8.5)	Irritation in rats at 40 ppm for 7 hr (Dunlap et al., 1958)
AEGL-3 (Lethality)	36 (87)	25 (61)	20 (48)	10 (24)	7.1 (17)	NOEL for lethality in mice, rats, and rabbits exposed to 200 ppm for 1 hr (Union Carbide, 1951)

References:

AIHA (American Industrial Hygiene Association). 1989. Odor Thresholds for Chemicals with Established Occupational Health Standards. AIHA, Fairfax, VA.

Dunlap, M.K., Kodama, J.K., Wellington, J.S., Anderson, H.H., and Hine, C.H. 1958. The toxicity of Allyl Alcohol. *American Medical Association Archives of Industrial Health* **18**:303-311.

ten Berge, W.F. 1986. Concentration-time mortality response relationship of irritant and systemically acting vapours and gases. *Journal of Hazardous Materials* **13**:301-309.

Torkelson, T.R., Wolf, M.A., Oyen, F., and Rowe, V.K. 1959a. Vapor toxicity of allyl alcohol as determined on laboratory animals. *American Industrial Hygiene Association Journal* **20**:224-229.

Union Carbide and Carbon Corporation. 1951. Initial submission: Letter from DuPont Chemical to U.S. EPA regarding a letter about toxicity studies with allyl alcohol with cover letter dated 10/15/92. Union Carbide and Carbon Corporation, New York, N.Y. Doc. # 88-920009857.

1. INTRODUCTION

Allyl alcohol is a colorless liquid that is a potent sensory irritant. The chemical has a pungent, mustard like odor, and the odor detection threshold is in the range of 1.4-2.1 ppm (AIHA, 1989). Primarily used in the production of allyl esters for use in resins and plasticizers, allyl alcohol is also used as an intermediate in the production of pharmaceuticals and other organic chemicals, as a fungicide and herbicide, in the production of glycerol, acrolein, and war gas, and as a flavoring agent (ACGIH, 1991; Budavari et al, 1996; Clayton and Clayton, 1994; Tabershaw et al., 1977). The physicochemical data of allyl alcohol are presented in Table 1.

Toxicity data in humans were limited studies with human volunteers. No lethality data or case reports of allyl alcohol exposure were available. Studies addressing lethal and nonlethal toxicity of allyl alcohol in several species of experimental animals were available.

TABLE 1. Chemical And Physical Data

Parameter	Value	Reference
Synonyms	2-propen-1-ol, 1-propenol-3, vinyl carbinol	Budavari et al., 1996
Molecular formula	C_3H_6O	Budavari et al., 1996
Molecular weight	58.08	Budavari et al., 1996
CAS Registry Number	107-18-6	ACGIH, 1991
Physical state	liquid	Budavari et al., 1996
Color	colorless	Budavari et al., 1996
Solubility	miscible with water, alcohol, chloroform, ether, petroleum ether	Budavari et al., 1996
Vapor pressure	23.8 mmHg at 25°C 17 torr at 20°C	Clayton and Clayton, 1994 ACGIH, 1991
Vapor density (Air=1)	2.0	Parmeggiani, 1983
Specific gravity (water = 1)	0.8540 @ 20/4°C	Budavari et al., 1996
Melting point	-50°C	Budavari et al., 1996
Boiling point	96-97°C	Budavari et al., 1996
Odor threshold	1.4-2.1 ppm pungent, mustard-like odor	AIHA, 1989 ACGIH, 1991
Conversion factors	1 ppm = 2.42 mg/m^3 1 mg/m^3 = 0.413 ppm	NIOSH, 1994a

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

There were no reported cases of death following exposure to allyl alcohol found in the literature searched.

2.2. Nonlethal Toxicity

2.2.1. Acute studies

Nonlethal toxicity in humans was associated with sensory irritation. Groups of five to seven volunteers, ranging in age from 19 to 39 years, were exposed to allyl alcohol in an exposure room from one to three times a week for 5 minutes (Dunlap et al., 1958). The exposure room was cubical with approximately an 18,000 liter volume, and had a revolving fan for mixing the vapors in the room. The vapors were generated by flash vaporization of allyl alcohol using a heat source. Five minutes of vaporization and equilibration were allotted before volunteers entered the room for the static exposure. It was not stated if the exposure concentrations were calculated or measured concentrations. Volunteers were "preconditioned at the beginning of the experiment by reviewing with them the different subjective sensations associated with a particular level of response... but the subject was not aware of the nature of the material." During the static exposure at one-minute intervals, they graded their responses to eye and nose irritation, olfactory recognition, central nervous system effects, and pulmonary effects as absent, slight, moderate, severe, or extreme (see Table 2). When reporting the results, however, the authors listed the responses as only slight or moderate or greater, with the exception of eye irritation. Olfactory recognition was noted as slight by 5 of 6 subjects at the lowest concentration of 0.78 ppm, and became at least moderate at 6.25 ppm in 2 of 6 subjects. At concentrations of 12.5 ppm, moderate or greater nose irritation was experienced by 4 of 7 volunteers, and all subjects expressed nose irritation as moderate or greater at 25.0 ppm. Eye irritation was not noted until 25.0 ppm, but was graded as severe. It was not stated if the responses varied with multiple exposures. Although not associated with the exposures of the volunteers, in the same paper Dunlap et al. (1958) described symptoms in workers who were exposed to "moderate" concentrations of allyl alcohol (range not given). The symptoms were comprised of lacrimation, retrobulbar pain, and blurred vision, and persisted for 24 to 48 hours after exposure. No permanent damage to the cornea was reported following exposure to allyl alcohol vapors.

TABLE 2. Summary of Sensory Response to Allyl Alcohol During 5-Minute Exposure [a]

Conc. (ppm)	No. Subjects	Olfactory Recognition		Eye Irritation		Nose Irritation	
		Slight	Moderate	Slight	Moderate	Slight	Moderate
0.78	6	5	1	0	0	2	0
6.25	6	4	2	1	0	3	1
12.5	7	6	1	1	0	3	4
25.0	5	3	1	0	5	0	5

[a] Data taken from Dunlap et al., 1958.

Ten volunteers were exposed to 2 ppm allyl alcohol for 1-3 minutes (Torkelson et al., 1959a). The volunteers went into a large chamber in groups of 2 or 3 once the desired concentration was obtained (methods in Torkelson et al., 1959b). Half of the volunteers reported a distinct odor but no irritation. McCord (1932) commented that workers exposed to allyl alcohol (concentrations and durations not reported) had signs and symptoms limited to severe irritation of the mucous membranes with edema and excessive secretions, conjunctivitis and lacrimation (specifics of exposures not given), and that exposure to 5 ppm allyl alcohol would produce some irritation. One worker was reportedly temporarily blinded by delayed corneal necrosis following exposure to the vapor, although the nature of the exposure was not provided (Smyth, 1956). Smyth stated that the primary toxic effect following exposure to allyl alcohol vapor is irritation manifested by pulmonary edema and disabling corneal injury.

Odor threshold values for allyl alcohol are reported by the American Industrial Hygiene Association (AIHA, 1989) as 1.4 ppm (3.3 mg/m^3) and 2.1 ppm (5 mg/m^3). These values are based on two studies (Katz and Talbert, 1930; Dravnieks, 1974; as cited in AIHA, 1989) that were critiqued by the AIHA and graded as acceptable.

2.2.2. Epidemiology Studies

Epidemiologic studies regarding human exposure to allyl alcohol were not available in the literature searched.

2.3. Developmental/Reproductive Effects

No data are available regarding the developmental/reproductive toxicity of allyl alcohol in humans.

2.4. Genotoxicity

No information on the genotoxicity of allyl alcohol in humans was available.

2.5. Carcinogenicity

No information on the potential carcinogenicity of allyl alcohol in humans was available.

2.6. Summary

There were no reported cases of death following allyl alcohol exposure in humans, and no case reports of accidental work exposures. Volunteers exposed to allyl alcohol for 5 minutes reported nose irritation at 12.5 ppm (nominal concentration), and severe eye irritation at 25 ppm (nominal concentration). Workers exposed to moderate concentrations (range not given) were reported to experience lacrimation, retrobulbar pain, and blurred vision. Accepted odor detection threshold values for allyl alcohol are 1.4- 2.1 ppm, and an odor detection of 0.78 ppm (nominal concentration) was reported.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

Acute lethality data were available for monkeys, rats, mice, and rabbits. Data are summarized in Table 3 and are described in greater detail in the following sections.

TABLE 3. Summary of Acute Lethal Inhalation Data in Laboratory Animals

Species	Conc. (ppm)	Exposure Time (h)	Effect	Reference
Monkey	1000	4	Death	McCord, 1932
Mouse	200	1	0/10 died	Union Carbide, 1951
Mouse	500	0.5 1	0/10 died 4/10 died	Union Carbide, 1951
Mouse	1000	1 2 4	6/10 died 8/10 died 10/10 died	Union Carbide, 1951
Mouse	2450-26,000	24-165 min	exposed until death	Shell Chemical Corporation, 1957
Mouse	22,000 12,200	10 min 2 x 10 min	10/10 died: 0/10 died first exposure; 10/10 died after second exposure	Shell Chemical Corporation, 1957
Rat	1060	1	LC_{50}	Dunlap et al., 1958; Dunlap and Hine, 1955
Rat	165	4	LC_{50}	Dunlap et al., 1958
Rat	76	8	LC_{50}	Dunlap et al., 1958
Rat	200	1	0/10 died	Union Carbide, 1951
Rat	1000	0.5 1 2	1/6 died 4/6 died 6/6 died	Union Carbide, 1951
Rat	1000	1	4/6 died	Smyth and Carpenter, 1948
Rat	1000	3	6/6 died during exposure	McCord, 1932
Rat	200	2 x 7h	4/4 died by end of 2nd exposure	McCord, 1932
Rat	50	7h/d, 30 days of exposure	4/5 died	McCord, 1932
Rat	60 100 150	7h/d, 5d/wk, for 60 exposures	1/10 by 60th exposure 6/10 by 56 exposure 10/10 by 10th exposure	Dunlap et al., 1958
Rabbit	200	1	0/10 died	Union Carbide, 1951
Rabbit	500	2 4	0/4 died 4/4 died	Union Carbide, 1951
Rabbit	1000	3.5 4.25	2/2 died during exposure; one at each exposure time given	McCord, 1932

3.1.1. Monkeys

One monkey (sex not given) exposed to 1000 ppm allyl alcohol for 7 hours died 4 hours after exposure (McCord, 1932). Prior to death, the monkey was vomiting, had diarrhea, and appeared

to be in severe pain. Necropsy revealed subcutaneous hemorrhage of the abdomen, petechial hemorrhage and inflammation of the intestine, a distended gastrointestinal tract, and hemorrhage of the spleen and kidneys. Inflammation was noted in the brain, meninges, and blood vessels, and the lungs showed edema with hemorrhagic exudate.

3.1.2. Rats

To calculate inhalation LC_{50} values for allyl alcohol in rats, groups of 6, male, Long-Evans rats were exposed to 40-2300 ppm allyl alcohol (individual concentrations not given) for 1, 4, or 8 hours in a cylindrical glass chamber having a capacity of 19.5 liters (Dunlap et al., 1958). There was no mention of a control group, and analysis of allyl alcohol vapor (in the chamber revealed that concentrations ranged from 15 to 25% less than nominal. Vapor concentrations were analyzed by drawing a sample of air through distilled water, adding bromine in acetic acid in the presence of mercapturic acetate as a catalyst, reducing the excess bromine with iodide, and then titrating the iodine with thiosulfate. Animals were observed for at least 10 days following exposure. The uncorrected 1, 4, and 8 hour LC_{50} values were 1060, 165, and 76 ppm, respectively. In this paper, Dunlap et al. reported the results of allyl alcohol toxicity in rats following various exposure routes, which included inhalation, intragastric administration, and intraperitoneal injection. The signs of toxicity and pathology changes were not separated for the various exposure routes, so it was not entirely clear if some signs of toxicity were specifically related to inhalation exposure, or if the signs were indeed independent of the method of exposure. The general signs of toxicity reported were lacrimation and tremors, ataxia, and coma preceding death. Pulmonary edema and congestion, visceral congestion, and discolored liver were found during necropsy. Microscopic examination showed liver damage consisting of congestion and necrosis. The idea that toxic signs and pathology changes are not dependent upon the exposure route of allyl alcohol was supported by the published abstract by Dunlap and Hine (1955). It was stated that allyl alcohol-induced lesions, such as necrosis, hemorrhage, and discoloration of the liver, discoloration of the kidneys, and congestion and hemorrhage of the intestines, did not vary with the route of administration. However, eye and nose irritation with profuse lacrimation was specifically noted with the single 1-hour inhalation exposures in rats (concentrations not given), from which the 1-hour LC_{50} value of 1060 ppm (also reported in Dunlap et al., 1958) was derived.

Six Sherman rats (sex not given) were exposed to 1000 ppm allyl alcohol vapor for 1 hour (no details about exposure conditions provided) and observed for 14 days for mortality (Smyth and Carpenter, 1948). Four of the six exposed rats died. Exposure concentration was not confirmed by analytical methods, and no controls were used.

McCord (1932) exposed rats (sex and strain not given) to several concentrations of allyl alcohol vapor for various time periods. Six rats (strain and sex not given) exposed to 1000 ppm allyl alcohol died after 3 hours of an intended 7-hour exposure. Results of the necropsy were not stated directly, but were said to be similar to the findings in the monkey (Section 3.1.1) and rabbits (Section 3.1.4) following allyl alcohol exposure. The primary findings in the rabbits and monkey were hemorrhage of the lungs, intestinal tract, bladder, and kidneys. Four rats exposed to 200 ppm allyl alcohol for 7 hours/day died on the first or second day of exposure, and necropsy revealed similar findings as described above. Four of five rats exposed to 50 ppm allyl alcohol for

7 hours/day died after approximately 30 days of exposure. Necropsy information was not given. No changes were observed in any of the control animals (number and treatment of control not given).

Union Carbide and Carbon Corporation (1951) submitted the mortality results of inhalation toxicity studies of allyl alcohol in rats to the U.S. EPA. No information was given about controls, method of exposure, strain or sex of rats, analytic verification of concentrations, or period of observation following exposure. The mortality results of the studies are presented in Table 4.

TABLE 4. Summary of Lethality Data in Rats Following Exposure to Allyl Alcohol [a]

Concentration (ppm)	Time (hour)	Deaths
200	1	0/10
1000	0.5	1/6
1000	1	4/6
1000	2	6/6

[a]Data taken from Union Carbide and Carbon Corporation, 1951.

In a series of three experiments, groups of 10 Long-Evans male rats were exposed to 1, 2, 5, 20, 40, 60, 100, or 150 ppm allyl alcohol vapor for 7 hours/day, 5 days/week, for a total of 60 exposures, and control groups were exposed to air (Dunlap et al., 1958). Analyses of the vapor concentrations at 40 ppm and greater were within 10% of nominal concentrations (information on the measured concentrations of the lower exposure concentrations not provided). Animals were observed daily and weighed weekly. At 90 days, the survivors were killed by decapitation and necropsied. Liver, kidney, and lungs from all animals were weighted and examined microscopically, while the thyroid, heart, thymus, pancreas, spleen, adrenal, testis, bladder and brain from every other animal were preserved for microscopic examination. Exposures to 1, 2, 5, and 20 ppm allyl alcohol did not produce any clinical signs of toxicity or abnormal gross or microscopic findings, although the animals in the 20 ppm group did have a statistically significant decrease in body weight gain. Rats exposed to 150 ppm exhibited gasping, severe depression, nasal discharge, and eye irritation. All of the 150 ppm rats died: four died during the first exposure, two following the first exposure, two during the second exposure, and two by the tenth exposure. The two rats surviving to the tenth exposure were lethargic, had red-rimmed eyes, and lost a third of their original body weight. Necropsy revealed hemorrhagic livers, pale and spotted lungs, and bloated gastrointestinal tracts. Slight congestion of the liver and lungs were found during microscopic evaluation. Rats exposed to 100, 60 or 40 ppm had similar but less intense signs, lesions, and microscopic findings. Six of the ten rats in the 100 ppm group died by 46 exposures, and the remaining rats were accidentally killed on exposure day 56. Gasping and muzzle rubbing occurred during the first few exposures to 60 ppm but disappeared thereafter, and persistent eye discharge was noted throughout the experiment. This group had statistically increased liver and kidney weights, and one death was recorded (date not given). All signs of irritation in animals exposed to 40 ppm disappeared after the first few exposures, but lung weight was statistically increased at necropsy.

Rats were exposed to 1, 5, 10, 20, 40, 60, 100, or 150 ppm allyl alcohol for a total of 60 eight-hour exposures over 90 days (information of strain, sex, and number not given) (Shell Chemical Corporation, 1957). No adverse effects were noted in animals exposed to 20 ppm or less. Decreased growth and mild to moderate lung congestion was noted in the 40 ppm group. Animals in the 60 ppm group had lung congestion and increased kidney and lung weights, and 1/10 animals died. All animals exposed to 100 ppm died after 32 exposures and rats exposed to 150 ppm died after 2 exposures.

3.1.3. Mice

Union Carbide and Carbon Corporation (1951) submitted the mortality results of inhalation toxicity studies of allyl alcohol in mice to the U.S. EPA. No information was given about controls, method of exposure, strain or sex of mice, analytic verification of concentrations, or the period of observation following exposure. The results of the studies are presented in Table 5.

TABLE 5. Summary of Lethality Data in Mice Following Exposure to Allyl Alcohol [a]

Concentration (ppm)	Time (h)	Deaths
200	1	0/10
500	0.5	0/10
500	1	4/10
1000	1	6/10
1000	2	8/10
1000	4	10/10

[a]Data taken from Union Carbide and Carbon Corporation, 1951.

Groups of 10 mice (species and sex not given) exposed to concentrations of 2450 to 26,000 ppm allyl alcohol died within a time range of 165 to 24 minutes, respectively (Shell Chemical Corporation, 1957). Before dying convulsively, all animals developed spastic paralysis of the extremities, particularly of the hindlimbs. Necropsy revealed irritation and inflammation of the respiratory tract and irritation and congestion of the liver, kidneys, and spleen. Death occurred in 10/10 mice exposed to 22,000 ppm for 10 minutes (no other details provided). No deaths resulted when mice were exposed to 12,200 ppm for 10 minutes, but all died when exposed for another 10 minute period (period of observation and time between exposures not given). When mice were exposed daily to 2450 ppm allyl alcohol for 10 minutes, 10% of the animals died by three exposures, and 30% were dead after nine exposures. Necropsy revealed irritation and inflammation of the respiratory tract and congestion of the gastrointestinal tract. Mice repeatedly exposed to 2450 ppm allyl alcohol were reported to develop severe eye and nose irritation.

3.1.4. Rabbits

Two rabbits (strain and sex not given) were exposed to 1000 ppm allyl alcohol. One rabbit died 3.5 hours into the exposure, and the other died 4.25 hours into the exposure (McCord, 1932). During the exposure, the rabbits had labored and noisy breathing, and fluid dripped from

their noses and mouths. Pulmonary hemorrhage, hemorrhage and inflammation of the intestinal tract, bladder, and kidneys, and gaseous distention of the gastrointestinal tract were noted in both rabbits during necropsy. One rabbit also had hemorrhaging of the eyes, opaque sclerae, and inflamed genitalia. In a second experiment, three rabbits were exposed to 200 ppm allyl alcohol for 7 hours/day. Labored and noisy breathing and discharge from the nose and mouth were observed within one hour of exposure. One rabbit convulsed and died after 3 days exposure, a second rabbit died after six days of exposure, and a third rabbit died after 18 days of exposure. The noisy and labored breathing and oral and nasal discharge continued with the exposures. Necropsy of the animals revealed similar findings to those described above. In a third experiment, two rabbits were exposed to 50 ppm allyl alcohol for 7 hours/day. One rabbit died after 14 exposures, and the second was killed after 28 exposures. Necropsy of the two rabbits revealed findings similar to those described above. No changes were observed in control animals (number and treatment of control not given).

Union Carbide and Carbon Corporation (1951) submitted the mortality results of inhalation toxicity studies of allyl alcohol in rabbits to the U.S. EPA. No information was given about controls, method of exposure, strain or sex of rabbits, analytic verification of concentrations, or the period of observation following exposure. The mortalities resulting from acute exposures are as follows: 0/10 exposed to 200 ppm for 1 hour; 0/4 exposed to 500 ppm for 2 hours, and 4/4 exposed to 500 ppm for 4 hours. The report also made the claim that exposure to 3400 ppm for 2 to 5 minutes will cause necrosis of the cornea of rabbits, but these data were not included.

3.2. Nonlethal Toxicity

Nonlethal toxicity data for allyl alcohol were available for dogs, rats, guinea pigs, rabbits, and mice. Data are summarized in Table 6 and are described in greater detail in the following sections.

TABLE 6. Summary of Sublethal Inhalation Data in Laboratory Animals

Species	Conc. (ppm)	Exposure Duration	Effects	References
Mouse	3.9	10 min	RD_{50}	Nielson et al., 1984
Mouse	2.5	10 min	RD_{50}	James et al., 1987
Mouse	2.4	6h/d, 4 d	Histopathological changes in upper respiratory epithelium, olfactory epithelium	Zissu, 1995
Rat	1 2 5	7h/d, 5d/wk, 60 exp.	No observable adverse effects	Dunlap et al., 1958
Rat	20	7h/d, 5d/wk, 60 exp.	No adverse effects except decrease in body weight gain	Dunlap et al., 1958
Rat	1 5 10 20	8h/d for 60 in 90 d	No adverse effects	Shell Chemical Co., 1957
Rat	40	7h/d, 5d/wk, 60 exp. in 90 d	Irritation (gasping, eye irritation, nasal discharge) disappeared after first few exposures; increased lung weight	Dunlap et al., 1958
Rat	40	8h/d for 60 exp. in 90 d	Decreased growth, mild to moderate lung congestion	Shell Chemical Co., 1957
Rat	60	7 h/d, 5d/wk, 60 exp. in 90 d	Irritation: gasping and muzzle rubbing first few exposures that disappeared thereafter; persistent eye discharge; increased lung and kidney weights; 1/10 died after 4 exp.	Dunlap et al., 1958
Rat	60	8h/d for 60 exp. in 90 d	Mild to moderate lung congestion, increased kidney and lung wts., 1/10 died	Shell Chemical Co., 1957
Rat, Guinea pig, Rabbit	7	7h/d, 5d/wk, 127-134 exp.	Reversible liver and kidney damage	Torkelson et al., 1959a
Rat, Guinea pig, Rabbit, Dog	2	7h/d, 5d/wk, 28 exp.	No adverse effects	Torkelson et al., 1959a

3.2.1. Dogs, Guinea Pigs, and Rabbits

Groups of 9 male and 9 female guinea pigs and 3 male and 3 female rabbits were exposed to 7 ppm (range of 6.6-7.1 ppm) allyl alcohol vapor for 28 seven-hour periods, to 2 ppm (range of 0.6-3.2 ppm) allyl alcohol vapor for 127-134 seven-hour periods, to control air, or were used as unexposed controls (Torkelson et al., 1959a; methods reported in Torkelson et al., 1959b). Groups of one male and one female beagle dog were also exposed to 2 ppm allyl alcohol, air, or used as unexposed controls. All exposures were for 7 hours/day, 5 days/week. None of the animals exposed to 7 ppm exhibited any clinical signs of toxicity or changes in body or organ weights, but microscopic examination found mild and reversible liver and kidney degeneration in almost all animals. Livers had dilation of the sinusoids, cloudy swelling, and focal necrosis, and kidneys showed epithelial necrosis in the convoluted tubules, proliferation of the interstitial tissue, and changes similar to those seen in glomerulonephritis. Animals exposed to 2 ppm allyl alcohol

vapor exhibited no measurable adverse effects from exposure as judged by clinical signs, mortality, body and organ weights, and gross and microscopic examination of tissues (noses not examined). (The species were not separated in this AEGL document because the data could not be adequately distinguished among the species tested),

3.2.2. Rats

As discussed in the lethality section (3.1.2), groups of 10 Long-Evans male rats were exposed in a series of three experiments to 1, 2, 5, 20, 40, 60, 100, or 150 ppm allyl alcohol vapor for 7 hours/day, 5 days/week, for a total of 60 exposures, and control groups were exposed to air (Dunlap et al., 1958). Analyses of the vapor at the higher concentrations were within 10% of nominal concentrations. Exposures to 1, 2, 5, and 20 ppm allyl alcohol did not produce any clinical signs of toxicity or abnormal gross or microscopic findings (noses not examined), although the animals in the 20 ppm group did have a statistically significant decrease in body weight gain. Mortality occurred in groups exposed to 60 ppm or higher. The animals exposed to 150 ppm exhibited gasping, severe depression, nasal discharge, and eye irritation, and necropsy revealed hemorrhagic livers, pale and spotted lungs, and bloated gastrointestinal tracts. Microscopic lesions consisted of slight congestion of the liver and lungs. It was stated that rats exposed to 40 - 100 ppm had similar but less intense signs, lesions, and microscopic findings noted in the 150 ppm group. No mortalities occurred in the 40 ppm group, and all signs of irritation disappeared after the first few exposures. Lung weight was statistically increased at necropsy.

Rats were exposed to 1, 5, 10, 20, 40, 60, 100, or 150 ppm allyl alcohol for a total of 60 eight-hour exposures over 90 days (information of strain, sex, and number not given; study discussed in Section 3.1.2) (Shell Chemical Corporation, 1957). No adverse effects were noted in animals exposed to 20 ppm or less. Decreased growth and mild to moderate lung congestion was noted in the 40 ppm group. Animals in the 60 ppm group had lung congestion and increased kidney and lung weights, and 1/10 animals died.

Groups of 12 male and 12 female rats were exposed to 7 ppm (range of 6.6-7.1 ppm) allyl alcohol vapor for 28 seven-hour periods, to 2 ppm (range of 0.6-3.2 ppm) allyl alcohol vapor for 127-134 seven-hour periods, to room air, or were used as unexposed controls (Torkelson et al., 1959a; methods reported in Torkelson et al., 1959b). All exposures were for 7 hours/day, 5 days/week. None of the animals exposed to 7 ppm exhibited any clinical signs of toxicity or changes in body or organ weights, but microscopic examination found mild and reversible liver and kidney degeneration in almost all animals. Livers had dilation of the sinusoids, cloudy swelling, and focal necrosis, and kidneys showed epithelial necrosis in the convoluted tubules, proliferation of the interstitial tissue, and changes similar to those seen in glomerulonephritis. Animals exposed to 2 ppm allyl alcohol vapor exhibited no measurable adverse effects from exposure as judged by clinical signs, mortality, body and organ weights, and gross and microscopic examination of tissues (noses not examined).

3.2.3. Mice

Groups of four male Ssc:CF-1 mice were exposed to 0.42, 2.00, 4.55, or 18.10 ppm allyl alcohol for 30 minutes to determine the RD_{50} for sensory irritation (Nielson et al., 1984). RD_{50}

values represent the concentration of an airborne sensory irritant that produces a 50% decrease in the respiratory rate, the decreased respiratory rate being caused by stimulation of the trigeminal nerve in the nasal mucosa. The animals were placed in a body plethysmograph attached to an exposure chamber such that the animal's head protruded into the chamber. Animals in the chambers were observed for 5 to 15 minutes to establish a baseline respiratory rate before beginning exposure to allyl alcohol. An RD_{50} value of 3.9 ppm (95% C.I.: 2.4-6.5 ppm) was determined based on the maximum decrease in respiratory rate within the first 10 minutes of exposure, and another value of 4.8 ppm (95% C.I.: 2.7-10.2 ppm) was given for the mean value for the last 10 minutes (exposure during the last 21-30 minutes). The onset of decreased respiratory rate occurred rapidly, plateaued within 10 minutes of exposure, and quickly subsided following termination of the exposure. Although studies investigating intravenous administration of allyl alcohol have demonstrated that conversion of allyl alcohol to acrolein is required to produce toxicity, this study did not find evidence of such a conversion occurring: there was no delay in the appearance, development, or disappearance of the irritant response. To determine if allyl alcohol produced pulmonary irritation at levels producing sensory irritation, concurrent exposures of tracheally cannulated mice to allyl alcohol were performed. These exposures did not reveal any pulmonary irritation occurring at the RD_{50} concentration producing sensory irritation.

James et al. (1987) reported an RD_{50} of 2.5 ppm allyl alcohol (2.0-3.2) for male ICR mice. Because the authors determined the 30-minute RD_{50} of allyl alcohol to verify their experimental system with that of already published methods, no specific information about the generation of the allyl alcohol RD_{50} was given: it is inferred to be the same as that given for the actual test compound, methylisocyanate vapor. Exposures were performed in glass exposure chambers, and vapor concentrations were measured by a gas analyzer. Animals were observed in the chambers for 10 minutes to establish a baseline respiratory rate, and were then exposed to allyl alcohol for 30 minutes.

Groups of ten male Swiss OF_1 mice were exposed to 2.4 or 6.4 ppm allyl alcohol for 6 hours/day for 4 days; 6 hours/day for 9 days (5 consecutive days the first week, 4 consecutive days the second week); or for 6 hours/day, 5 days/week for 2 weeks (Zissu, 1995). The target (nominal) concentrations were based on an RD_{50} value of 1.6 ppm, and 3 times the RD_{50} value of 4.8 ppm. Groups of 5 mice were used for controls. Histopathological examination of animals following the respective exposure durations revealed that lesions of the upper respiratory tract epithelium (hyperplasia, inflammatory infiltrates, and desquamation of some epithelial cells) and olfactory epithelium (a slight loss of isolated sensory cells) had developed in the 2.4 and 6.4 ppm groups. The lesions were most severe in the group exposed for 4 days, becoming less severe in the animals exposed for longer periods. No pathologic changes were noted in the trachea or lungs of exposed animals. The target RD_{50} of 1.6 was chosen from a published review (Bos et al., 1992) that summarized sensory irritation data for a large number of chemicals. The original reference (Muller and Greff, 1984) investigated the correlation between selected physio-chemical parameters and sensory irritation for four chemical groups.

3.3. Developmental/Reproductive Effects

A study by Jenkinson and Anderson (1990) evaluated the potential developmental and reproductive effects following allyl alcohol administration in rats. Six male Sprague-Dawley rats were dosed with 25 mg/kg for 4 weeks, and then 5.1 mg/kg from week 5 to week 11. Males were mated with virgin females on weeks 1-11 of treatment. Mating was confirmed when females tested positive for sperm. The females were killed on day 20 of pregnancy. There were no observed fetal malformations or karyotype abnormalities in fetuses of litters sired by the male rats treated with allyl alcohol, and no evidence of changes in reproductive parameters in exposed male rats.

Developmental toxicity of allyl alcohol was assessed in Sprague-Dawley rats (Slott and Hales, 1985). Fetuses were exposed to 10, 100, or 1000 µg allyl alcohol/fetus by intraamniotic injection on day 13 of gestation, and dams were killed and fetuses evaluated on day 20 of gestation. There was a dose-dependent increase in the incidence of fetal resorption, with doses of 100 and 1000 µg/fetus reaching statistical significance. Treatment with 1000 µg/fetus also resulted in a significant decrease in average fetal weight.

3.4. Genotoxicity

Allyl alcohol tested positive for mutagenicity in cultured V79 cells, having the same potency as acrolein (Smith et al., 1990). A positive test was obtained in a modified Ames assay (tester strain TA100) without metabolic activation, but the mutagenic activity was greatly reduced with metabolic activation. It has been suggested that bacterial alcohol dehydrogenase converts allyl alcohol to acrolein, which may be responsible for the mutagenic activity, and that the addition of the S9 mix inactivates acrolein by binding of the metabolite by the amino and sulfhydryl groups present in the mix (Lutz et al., 1982). Allyl alcohol tested positive for mutagenesis at concentrations of 50-300 µg/plate in the *Salmonella* tester strain TA1535 in the presence of hamster S9, but not in the presence of rat S9, and was not mutagenic in strains TA1537, TA1538, TA98, or TA100 in the presence or absence of rat or hamster S9 (Lijinsky and Andrews, 1980). Bignami et al. (1977) reported negative results in *Salmonella typhimurium* strains TA1535, TA100, TA1538, and TA98 (details not given), and allyl alcohol did not induce point mutations in *Aspergillus midulans*.

3.5. Carcinogenicity

Allyl alcohol has not been classified as to its carcinogenicity by the U.S. EPA or by IARC. No evidence of carcinogenicity was found in a study in which male and female F344 rats were administered 300 mg allyl alcohol/L in drinking water for 106 weeks, or when male and female hamsters were gavaged with 2 mg allyl alcohol for 60 weeks (Lijinsky and Reuber, 1987).

3.6. Summary

Exposure to 1000 ppm for as little as 0.5 hours to 4 hours resulted in mortality in monkeys, mice, rats, and rabbits. Mice survived exposure to 500 ppm for 0.5 hours but not 1 hour, and rabbits survived a 2-hour but not a 4-hour exposure. Mice, rats, and rabbits survived exposure to 200 ppm for 1 hour. The only LC_{50} values available were based upon target concentrations, and were unreliable as the author stated that actual concentrations ranged from 15-25% less than target concentrations. The uncorrected LC_{50} values in rats were 1060 ppm for 1 hour, 165 ppm

for 4 hours, and 76 ppm for 8 hours. Repeated exposures of rats to 60, 100, or 150 ppm for 7 hours/day, 5 days/week, for 60 exposures resulted in mortality.

Data on nonlethal, single inhalation exposures to allyl alcohol were limited to two RD_{50} studies in mice, in which RD_{50} values of 3.9 and 2.5 ppm were given. The studies were conducted in male Ssc:CF-1 mice and male ICR mice, respectively. Substantial differences have been observed between species in their response to irritants, and for this reason the standard RD_{50} testing protocol calls for the use of male Swiss-Webster mice only (Alarie et al., 1980; Annual Book of Standards, 1991). Therefore, the RD_{50} values generated in these two studies are questionable for use in AEGL derivations.

One study found histopathological lesions in the upper respiratory tract epithelium and olfactory epithelium of mice following exposure to 2.4 ppm for 6 hours/day for 4 days, and the lesions decreased in severity in groups exposed for 9 days or 2 weeks. Repeated inhalation exposures in rats to 1, 2, 5, and 20 ppm produced no gross toxicity, but repeated exposures to 40 ppm resulted in irritation that disappeared after the first few exposures and increased lung weights. Repeated inhalation exposures in rats, guinea pigs, rabbits, and dogs revealed no measurable adverse effects following 28, seven-hour exposures to 2 ppm, and rats, guinea pigs, and rabbits exposed to 7 ppm for 127-134 seven-hour exposures exhibited only mild and reversible microscopic liver and kidney damage. Allyl alcohol does not appear to be a potent developmental or reproductive toxicant or carcinogen, but has tested positive as a genotoxicant in some testing systems.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Mechanism of Toxicity

Signs of toxicity following inhalation exposures to allyl alcohol include lacrimation, pulmonary edema and congestion, and inflammation and hemorrhage of the liver and kidney. Histopathological examination of tissues from animals exposed to high concentrations of vapor have indicated that the alcohol is rapidly distributed, causing pulmonary congestion leading to edema and compensatory emphysema, and degeneration of the cells in the convoluted tubules of the kidney, liver, myocardium, ganglion cells of the spinal cord, and of the retina (McCord, 1932). Much attention has been focused on how allyl alcohol causes periportal necrosis in the liver of rats. It is unclear from the available inhalation toxicity studies if this effect is also present following this route of exposure, or is more apt to occur after oral, intraperitoneal, or intravenous administration. The studies on the mechanism of allyl alcohol-induced liver necrosis and covalent binding to liver macromolecules have disclosed that metabolism of allyl alcohol to the reactive metabolite acrolein is required (Serafini-Cessi, 1972; Patel et al., 1983). This reaction is mediated by the cytosolic liver enzyme alcohol dehydrogenase (ADH) in the presence of NAD^+. Consequently, the levels of ADH play an important role in hepatotoxicity of allyl alcohol. It was found that old male rats were more susceptible to allyl alcohol-induced hepatotoxicity than were young, adult, male rats because the old rats had increased ADH activity. Female rats were more sensitive than males, but were not affected by age (Rikans and Moore, 1987). Acrolein can be detoxified by further metabolism to acrylic acid by aldehyde dehydrogenase or by conjugation with glutathione (GSH) (Rikans, 1987; Rikans and Moore, 1987).

Because one of the primary routes of exposure to allyl alcohol is through inhalation, Patel et al. (1980) compared the metabolism of allyl alcohol in lung and liver preparations from male Holtzman rats. In the lungs, allyl alcohol was rapidly epoxidized to glycidol, and then further metabolized to glycerol, most likely by the action of epoxide hydrase (see Figure 1).

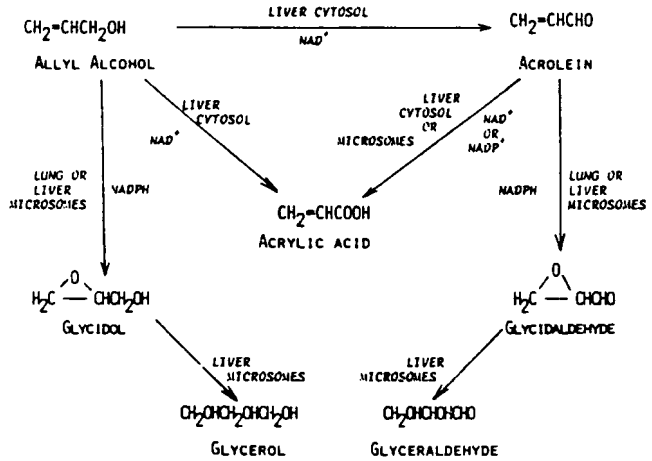

Figure 1 Metabolism of allyl alcohol and acrolein by liver and lung preparations. (Taken from Patel et al., 1980.)

Importantly, allyl alcohol was not metabolized to the reactive metabolite acrolein because the lungs do not contain ADH. Conversely, the liver preparations were able to metabolize allyl alcohol to a variety of metabolites; predominantly acrolein, acrylic acid, glycidaldehyde, and glyceraldehyde. It is not likely that much glycidol and glycerol would be produced in the liver, as most of the allyl alcohol would converted to acrolein.

No quantitative information was available on the absorption and distribution of allyl alcohol following inhalation exposure. Although studies investigating intravenous administration of allyl alcohol have demonstrated that conversion of allyl alcohol to acrolein is required to produce toxicity, the study by Nielson et al. (1984) did not find evidence of such a conversion occurring: there was no delay in the appearance, development, or disappearance of the measured irritant response in mice. The *in vitro* study by Patel et al. (1980) demonstrated that the lungs will not metabolize allyl alcohol to the reactive metabolite acrolein, but it is not known how much of the allyl alcohol will be distributed to the liver where the metabolic conversion will occur. The study investigating lung pathology in mice following repeated exposure to an RD_{50} concentration (Zissu, 1995) unfortunately did not investigate whether any pathologic changes had occurred in other organs such as the liver and kidney. Therefore, it is not known if inhalation exposures to lower concentrations of allyl alcohol will produce toxicity confined in the lungs, or if some systemic toxicity will also be produced. It should again be noted that subchronic exposures in rats, guinea pigs, and rabbits to 2 ppm allyl alcohol did not result in any measurable adverse effects (Torkelson, 1959a).

4.2. Structure-Activity Relationships

Structure-activity relationships were not used for derivation of AEGL values for allyl alcohol.

4.3. Species and Sex Differences

It is unclear from the available data as to which species is the most sensitive to allyl alcohol toxicity. Jacobs et al. (1987) found that male rats were more sensitive than male mice to allyl alcohol-induced hepatotoxicity following intraperitoneal administration of the chemical, but it is not known if the same effect would be observed following inhalation exposure. Rikans and Moore (1987) showed that female rats were more sensitive to allyl alcohol-induced hepatotoxicity than male rats, and old male rats were more sensitive than young adult male rats. The lethality data (summarized in Table 3) lack robust LC_{50} values, so a direct comparison of the sensitivity of the various species based upon LC_{50} values is not possible. The data do show that exposure to 1000 ppm for as little as 0.5 to 4 hours resulted in mortality in 4 species (monkeys, mice, rats and rabbits); exposure to 500 ppm was lethal in mice and rabbits at 1 and 4 hours, respectively. However, exposure to 200 ppm for 1 hour was not lethal in mice, rats, or rabbits. No effects were seen in dogs, rats, guinea pigs, or rabbits repeatedly exposed to 2 ppm, and only mild and reversible effects were seen in rats, guinea pigs, and rabbits repeatedly exposed to 7 ppm. These data suggest that not much variation exists across species in response to inhalation exposure to allyl alcohol.

5. RATIONALE AND PROPOSED AEGL-1

5.1. Human Data Relevant to AEGL-1

Human volunteers exposed to allyl alcohol for 5 minutes experienced nose irritation at 12.5 ppm, severe eye irritation at 25 ppm, and detected an odor at 0.78 ppm, with 2 of 6 subjects reporting mild nose irritation (Dunlap et al., 1958). Torkelson et al. (1959a) reported that 5/10 volunteers exposed to 2 ppm for 1-3 minutes detected a distinct odor but experienced no irritation. The accepted odor detection threshold values for allyl alcohol are 1.4 and 2.1 ppm (AIHA, 1989).

5.2. Animal Data Relevant to AEGL-1

No available animal data were appropriate for an AEGL-1 derivation.

5.3. Derivation of AEGL-1

Although the human exposures by Dunlap et al. (1958) measured some endpoints consistent with the definition of an AEGL-1, the exposures were of too short a duration to be reliable and the exposure concentrations were most likely nominal concentrations. If one were to use this study to derive an AEGL-1 based on nose irritation occurring at 12.5 ppm, and divide the human data by an uncertainty factor of 3 to account for differences in sensitivity between individuals (intraspecies) and scale across time, one ends up with values which are lower than the odor thresholds (see Table 12 in Appendix B). Therefore, the proposed AEGL-1 values will be based on the mean odor detection threshold value of 1.8 (AIHA). Because odor threshold is not dependent upon the length of exposure, the threshold value is applied to all times.

AEGL-1 values are presented in Table 7.

TABLE 7. Proposed AEGL-1 Values For Allyl Alcohol [ppm(mg/m^3)]

Classification	10-minute	30-minute	1-hour	4-hour	8-hour
AEGL-1	1.8 (4.4)	1.8 (4.4)	1.8 (4.4)	1.8 (4.4)	1.8 (4.4)

6. RATIONALE AND PROPOSED AEGL-2

6.1. Human Data Relevant to AEGL-2

No human data were appropriate for the derivation of an AEGL-2.

6.2. Animal Data Relevant to AEGL-2

No single-exposure inhalation studies reported effects that were consistent with the AEGL-2 definition. Repeated 7-hour exposures of rats to 20, 40, or 60 ppm allyl alcohol resulted in no measurable adverse effects at 20 ppm; irritation which disappeared after the first few exposures and increased lung weight at necropsy after exposure to 40 ppm; and irritation (gasping and muzzle-rubbing) which disappeared after the first few exposures, persistent eye discharge, and one death when exposed to 60 ppm (Dunlap et al., 1958). Repeated 8-hour exposures of rats to 40 ppm resulted in only moderate lung congestion (Shell Chemical Corporation, 1992).

6.3. Derivation of AEGL-2

Although AEGL values are normally based on single-exposure studies, no single-exposure studies were appropriate for derivation of the allyl alcohol AEGL-2. In a subchronic exposure study, rats repeatedly exposed to 40 ppm for 7 hours/day experienced irritation during the first few exposures that disappeared thereafter (Dunlap et al., 1958). This experiment provides the basis for the AEGL-2 derivation.

An uncertainty factor of 3 was applied for species to species extrapolation because there did not appear to be much variation between species: a NOEL for lethality was the same for 3 different species (mice, rats, and rabbits). An uncertainty factor of 3 was also applied for intra-species extrapolation. Although the traditional approach for uncertainty factors in a case such as this would argue for an uncertainty factor of 10 because of the lack of data addressing inter-individual variability, this would result in a composite uncertainty factor of 30. An uncertainty factor of 30 would drive the AEGL-2 values to a level that would be inconsistent with available data (8 hour AEGL-2 of 1.2 ppm): Dunlap et al. (1958) reported that rats exposed for 7 hr/d, 5 days/wk for 60 exposures to 1, 2, or 5 ppm had no observable adverse effects, while rats repeatedly exposed to 20 ppm only exhibited decreased body weight gain, and Torkelson et al. (1959a) reported that no adverse effects were noted when rats, guinea pigs, rabbits, and dogs were exposed to 2 ppm for 7 hr/d, 5 d/wk for 28 exposures, while exposure of rats, guinea pigs, and rabbits exposed to 7 ppm for 7 hr/d, 5 d/wk for 134 exposures exhibited only reversible liver and kidney damage. Therefore, a total uncertainty factor of 10 was applied to the AEGL-2 value.

The experimentally derived exposure value was then scaled to AEGL time frames using the concentration-time relationship given by the equation $C^n \times t = k$, where C = concentration, t = time, k is a constant, and n generally ranges from 1 to 3.5 (ten Berge, 1986). The value of n was not empirically derived due to the unreliability and inconsistencies of the data; therefore, the default value of $n = 1$ was used for extrapolating from shorter to longer exposure periods and a value of n = 3 was used to extrapolate from longer to shorter exposure periods. The 10-minute value was set equal to the 30-minute value because it was considered too precarious to extrapolate from the exposure duration of 7 hours to 10 minutes.

AEGL-2 values are presented in Table 8.

TABLE 8. Proposed AEGL-2 Values For Allyl Alcohol [ppm(mg/m^3)]

Classification	10-minute	30-minute	1-hour	4-hour	8-hour
AEGL-2	9.6 (23)	9.6 (23)	7.7 (19)	4.8 (12)	3.5 (8.5)

The derivation is further supported by the Shell Chemical Corporation (1992) study in which repeated 8-hour exposures of rats to 40 ppm resulted in only moderate lung congestion.

7. RATIONALE AND PROPOSED AEGL-3

7.1. Human Data Relevant to AEGL-3

No human data were relevant for the derivation of an AEGL-3. No reports of death following accidental exposure to allyl alcohol were found in the available literature.

7.2. Animal Data Relevant to AEGL-3

Mice, rats, and rabbits survived exposures to 200 ppm for 1 hour; mice survived exposure to 500 ppm for 0.5 hours, but not 1 hour; and rabbits survived a 2 hour but not a 4 hour exposure (Union Carbide, 1951). One set of LC_{50} values were determined. However, these values were unreliable because the authors stated that the actual exposure concentrations were 15-25% less than the target concentrations, yet they did not give the corrected concentrations (Dunlap et al., 1958). Other animal data showed that exposure to 1000 ppm for as little as 0.5 hours to 4 hours resulted in mortality in monkeys, mice, rats, and rabbits (McCord, 1932; Union Carbide, 1951; Smyth and Carpenter, 1948).

7.3. Derivation of AEGL-3

Because the LC_{50} studies were unreliable and the rest of the data did not permit calculation of a dependable concentration-response relationship, a NOEL for lethality in mice, rats, and rabbits of 200 ppm for 1 hour was chosen as the AEGL-3 endpoint (Union Carbide, 1951).

An uncertainty factor of 3 was applied for species to species extrapolation because there did not appear to be much variation between species for lethality. A NOEL for lethality was the same for 3 different species (mice, rats, and rabbits), and this endpoint was used for the AEGL-3 derivation. Additionally, the use of a NOEL for lethality is inherently conservative An uncertainty factor of 3 was also applied for intraspecies extrapolation. Although the traditional approach for uncertainty factors in a case such as this would argue for an uncertainty factor of 10 because of the lack of data addressing interindividual variability, this would result in a composite uncertainty factor of 30. An uncertainty factor of 30 would drive the AEGL-3 values to a level that would be inconsistent with available data (1 hour AEGL-3 of 6.7 ppm): Dunlap et al. (1958) reported that rats exposed for 7 hr/d, 5 days/wk for 60 exposures to 1, 2, or 5 ppm had no observable adverse effects, while rats exposed to 20 ppm only exhibited decreased body weight gain, and Torkelson et al. (1959a) reported that no adverse effects were noted when rats, guinea pigs, rabbits, and dogs were exposed to 2 ppm for 7 hr/d, 5 d/wk for 28 exposures, while exposure of rats, guinea pigs, and rabbits exposed to 7 ppm for 7 hr/d, 5 d/wk for 134 exposures exhibited only reversible liver and kidney damage. Therefore, a total uncertainty factor of 10 was applied to the AEGL-3 value.

The experimentally derived exposure value was then scaled to AEGL time frames using the concentration-time relationship given by the equation $C^n \times t = k$, where C = concentration, t = time, k is a constant, and n generally ranges from 1 to 3.5 (ten Berge, 1986). The value of n was not empirically derived due to the unreliability and inconsistencies of the data; therefore a default value of n should be used in the temporal scaling of AEGL values across time. If one applies the default value of $n = 1$ for extrapolating from shorter to longer exposure periods and a value of n = 3 to extrapolate from longer to shorter exposure periods, one obtains the values in Table 9.

TABLE 9. AEGL-3 Values For Allyl Alcohol (using a default of n=1 for shorter to longer exposure periods and n=3 for longer to shorter exposure periods)					
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**
AEGL-3	36 ppm	25 ppm	20 ppm	5.0 ppm	2.5 ppm

Again, going with a default value results in AEGL values that are inconsistent with the available data. The AEGL-2 data do not support the selection of a value of n=1 for extrapolation to 4 or 8 hours: when using an n=1 (which assumes a "conservative" scenario) to extrapolate from 1 hour to 4 or 8 hours, one obtains a 4-hour AEGL-3 value of 5.0 ppm, which is almost identical to the 4-hour AEGL-2 value of 4.8 ppm, and an 8-hour AEGL-3 value of 2.5 ppm, which is lower than the 8-hour AEGL-2 value of 3.5 ppm. The AEGL-2 values help to serve as a baseline: they are based on a multiple exposure scenario in which rats exposed for 40 ppm for 7 hrs/d exhibited reversible signs of irritation. It is unreasonable to have an AEGL-3 values below the AEGL-2 values. Therefore, in the absence of any further data, an *n* of 2 was selected as a reasonable compromise between the possible values for *n* as reported by ten Berge (1986): it is between the most conservative *n*=1 (which results in unreasonable values) and an *n* of 3, a least conservative value. AEGL-3 values based on an n=3 for extrapolation from 1 hour to 10 and 30 minutes and an n=2 for extrapolation from 1 hour to 4 or 8 hours are presented in Table 10.

TABLE 10. Proposed AEGL-3 Values for Allyl Alcohol					
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**
AEGL-3	36 (87)	25 (61)	20 (48)	10 (24)	7.1 (17)

The study in which mice survived a 500 ppm exposure for 0.5 hours produces similar but slightly higher values.

8. SUMMARY OF PROPOSED AEGLs

8.1. AEGL Values and Toxicity Endpoints

A summary of the proposed AEGL values for allyl alcohol are summarized in Table 11. The AEGL-1 is based on the odor threshold of the chemical. Irritation noted during the first few exposures in a subchronic study was used for the AEGL-2. The AEGL-3 was based on a NOEL for lethality.

TABLE 11. Summary of Proposed AEGL Values [ppm(mg/m^3)]					
Classification	**Exposure Duration**				
	10-minute	**30-minute**	**1-hour**	**4-hour**	**8-hour**
AEGL-1 (Nondisabling)	1.8 (4.4)	1.8 (4.4)	1.8 (4.4)	1.8 (4.4)	1.8 (4.4)
AEGL-2 (Disabling)	9.6 (23)	9.6 (23)	7.7 (19)	4.8 (12)	3.5 (8.5)
AEGL-3 (Lethal)	36 (87)	25 (61)	20 (48)	10 (24)	7.1 (17)

8.2. Comparisons with Other Standards

Standards and guidance levels for workplace and community exposures are listed in Table 12. The AEGL-1 value is slightly below the ACGIH TLV-TWA and the NIOSH and OSHA TWA. The 1-hour AEGL-3 is the same as the IDLH.

TABLE 12. Extant Standards and Guidelines for Allyl Alcohol					
Guideline	**Exposure Duration**				
	10-minute	**30-minute**	**1-hour**	**4-hour**	**8-hour**
AEGL-1	1.8 ppm	1.8 ppm	1.8 ppm	1.8 ppm	1.8 ppm
AEGL-2	9.6 ppm	9.6 ppm	7.7 ppm	4.8 ppm	3.5 ppm
AEGL-3	36 ppm	25 ppm	20 ppm	10 ppm	7.1 ppm
NIOSH IDLH [a]	20 ppm				
NIOSH REL [b]					Cancer; lowest feasible concentration
OSHA PEL-TWA [c]					2 ppm; [5 mg/m^3]
OSHA STEL [skin] [c]					4 ppm
ACGIH TWA [d]					0.5 ppm; [1.21 mg/m^3]
MAK (German) [e]					not established: may be carcinogenic to man
MAC (Dutch) [f]					5 mg/m^3; [2 ppm]

[a]NIOSH 1994, 1999
[b]NIOSH 1999
[c]NIOSH, 1987
[d]ACGIH 2000
[e]German Research Association, 1999
[f]Ministry of Social Affairs and Employment, 2000

8.3. Data Adequacy and Research Needs

Data available for AEGL derivations were limited. Although there were human exposures in which sensory irritation was measured, the exposure durations were limited to 5 minutes, therefore rendering them inappropriate for scaling across time. No other human data were available.

Animal data were limited to studies in which lethality was the only endpoint of interest, sub-chronic exposures, or single-exposure experiments in which the model was questionable.

9. REFERENCES

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APPENDIX A: Derivation of AEGL Values

DERIVATION OF AEGL-1 VALUES

Key study: AIHA, 1989

Toxicity endpoint: mean odor detection threshold at 1.8 ppm

Scaling: none

Uncertainty factors: none

10-min, 30-min, 1-hr, 4-hr, and 8-hr AEGL-1: 1.8 ppm; threshold value applied to all times

DERIVATION OF AEGL-2 VALUES

Key study: Dunlap et al., 1958

Toxicity endpoint: Irritation in rats repeatedly exposed to 40 ppm allyl alcohol vapor for 7 hours: signs disappeared after first few exposures

Scaling: $C^n \times t = k$ (default of n=1 for shorter to longer exposure periods and n=3 for longer to shorter exposure periods)
$(40 \text{ ppm})^1 \times 7 \text{ hr} = 280 \text{ ppm hr}$
$(40 \text{ ppm})^3 \times 7 \text{ hr} = 448000 \text{ ppm hr}$

Uncertainty factors: 3 for interspecies variability
3 for intraspecies variability
Combined uncertainty factor of 10

10-minute AEGL-2 Inappropriate to scale from 7 hr to 10 min; the 10-min value was set equal to the 30 min value

10-min AEGL-2 = 9.6 ppm

30-minute AEGL-2
$C^3 \times 0.5 \text{ hr} = 448000 \text{ ppm hr}$
$C^3 = 896000 \text{ ppm}$
C = 96.4 ppm
30-min AEGL-2 = 96.4 ppm/10 = 9.6 ppm

1-hour AEGL-2
$C^3 \times 1 \text{ hr} = 448000 \text{ ppm hr}$
$C^3 = 448000 \text{ ppm}$
C = 76.5 ppm
1-hr AEGL-2 = 76.5 ppm/10 = 7.7 ppm

4-hour AEGL-2
$C^3 \times 4 \text{ hr} = 448000 \text{ ppm hr}$
$C^3 = 112000 \text{ ppm}$
C = 48.2 ppm
4-hr AEGL-2 = 48.2 ppm/10 = 4.8 ppm

8-hour AEGL-1
$C^1 \times 8 \text{ hr} = 280 \text{ ppm hr}$
$C^1 = 35 \text{ ppm}$
C = 35 ppm
8-hr AEGL-2 = 35 ppm/10 = 3.5 ppm

DERIVATION OF AEGL-3 VALUES

Key study: Union Carbide, 1951

Toxicity endpoint: NOEL for lethality: mice, rats, and rabbits survived 1 hour exposure to 200 ppm

Scaling: $C^n \times t = k$ (default n=3 for longer to shorter exposure periods; and use of n=2 for shorter to longer exposure periods; see document)
$(200\ ppm)^2 \times 1\ hr = 40{,}000\ ppm\ hr$
$(200\ ppm)^3 \times 1\ hr = 8{,}000{,}000\ ppm\ hr$

Uncertainty factors: 3 for interspecies variability
3 for intraspecies variability
Combined uncertainty factor of 10

10-minute AEGL-3
$C^3 \times 0.0.167\ hr = 8{,}000{,}000\ ppm\ hr$
$C^3 = 47904192\ ppm$
$C = 363.2\ ppm$
10-min AEGL-3 = 363.2 ppm/10 = 36 ppm

30-minute AEGL-3
$C^3 \times 0.5\ hr = 8{,}000{,}000\ ppm\ hr$
$C^3 = 16{,}000{,}000\ ppm$
$C = 252.0\ ppm$
30-min AEGL-3 = 252.0 ppm/10 = 25 ppm

1-hour AEGL-3
$C^2 \times 1\ hr = 40{,}000\ ppm\ hr$
$C^2 = 40{,}000\ ppm$
$C = 200\ ppm$
1-hr AEGL-3 = 200 ppm/10 = 20 ppm

4-hour AEGL-3
$C^2 \times 4\ hr = 40{,}000\ ppm\ hr$
$C^2 = 10{,}000\ ppm$
$C = 100\ ppm$
4-hr AEGL-3 = 100 ppm/10 = 10 ppm

8-hour AEGL-3
$C^2 \times 8\ hr = 40{,}000\ ppm\ hr$
$C^2 = 5{,}000\ ppm$
$C = 70.7\ ppm$
8-hr AEGL-3 = 70.7 ppm/10 = 7.1 ppm

APPENDIX B: Derivation Summary for Allyl Alcohol AEGLs

ACUTE EXPOSURE GUIDELINE LEVELS FOR ALLYL ALCOHOL (CAS Reg. No. 107-18-6) DERIVATION SUMMARY

AEGL-1 VALUES				
10-minute	**30-minute**	**1-hour**	**4-hour**	**8-hour**
1.8 ppm	**1.8 ppm**	**1.8 ppm**	**1.8 ppm**	**1.8 ppm**

Key Reference: AIHA (American Industrial Hygiene Association). 1989. Odor Thresholds for Chemicals with Established Occupational Health Standards. AIHA, Fairfax, VA.

Test Species/Strain/Number: Humans

Exposure Route/Concentrations/Durations: Inhalation

Effects: Mean odor detection threshold

Endpoint/Concentration/Rationale: Mean odor detection threshold of 1.8 ppm (mean of 1.4 and 2.1 ppm)

Uncertainty Factors/Rationale:
Total uncertainty factor: NA (1)
Interspecies: NA (1) - human data used
Intraspecies: NA (1) - odor threshold

Modifying Factor: NA (1)

Animal to Human Dosimetric Adjustment: NA - human data used

Time Scaling: NA - odor is a threshold effect; therefore, the threshold value was applied to all time points

Comments:

AEGL-2 VALUES				
15-minute	**30-minute**	**1-hour**	**4-hour**	**8-hour**
9.6 ppm	**9.6 ppm**	**7.7 ppm**	**4.8 ppm**	**3.5 ppm**

Key Reference: Dunlap, M.K., Kodama, J.K., Wellington, J.S., Anderson, H.H., and Hine, C.H. 1958. The toxicity of allyl alcohol. A.M.A. Arch. Ind. Health 18: 303-311.

Test Species/Strain/Sex/Number: Male Long-Evans rats, 10/exposure group

Exposure Route/Concentrations/Durations: 0, 1, 2, 5, 20, 40, 60, 100, or 150 ppm for 7 hours/day, 5 days/week, for 60 exposures

Effects:

1, 2, 5 ppm	No observable adverse effects
20 ppm	Only observable effect was decreased body weight
40 ppm	Irritation: gasping, eye irritation, nasal discharge disappeared after first few exposures; increased lung weight
60 ppm	Irritation: gasping and muzzle rubbing first few exposures that disappeared thereafter; persistent eye discharge; increased lung and kidney weights; 1/10 died after 4th exposure
100 ppm	6/10 died
150 ppm	10/10 died

Endpoint/Concentration/Rationale: Exposure to 40 ppm for 7 hours/day resulted in irritant effects during the first few exposures that disappeared thereafter

Uncertainty Factors/Rationale:
Total uncertainty factor: 10
Interspecies: 3- does not appear to be much variation across species in their response to allyl alcohol (lethality)
Intraspecies: 3 - data support use of 3 (see "Comments")

Modifying Factor: NA (1)

Animal to Human Dosimetric Adjustment: Insufficient data

Time Scaling: $C^n \times t = k$ where n = 3 for extrapolation from longer to shorter durations (30 min, 1, 2, and 4 hr) and n=1 for extrapolation from shorter to longer durations (8 hr). 10-min value was set equal to the 30 min value because it is considered to precarious to extrapolate from 7 hr to 10 min

Comments: Use of selected value of 10 for intraspecies uncertainty factor and default value of n=3 for extrapolation from shorter to longer time periods results in values that are inconsistent with available toxicity data for allyl alcohol; therefore, values of n = 3 and 2, respectively, were justified

AEGL-3 VALUES				
10-minute	**30-minute**	**1-hour**	**4-hour**	**8-hour**
36 ppm	**25 ppm**	**20 ppm**	**10 ppm**	**7.1 ppm**

Key Reference: Union Carbide and Carbon Corporation. 1951. Initial submission: Letter from DuPont Chem to USEPA regarding a letter about toxicity studies with allyl alcohol with cover letter dated 10/15/92. Union Carbide and Carbon Corporation, New York, N.Y. Doc. # 88-920009857.

Test Species/Strain/Sex/Number: Groups of 6 or 10 rats; 10 mice; 4 or 10 rabbits

Exposure Route/Concentrations/Durations: Inhalation: for concentrations and durations see below:

Effects:

Species	Time (hr)	Conc. (ppm)	Mortality
Rat	1	200	0/10
	0.5	1000	1/6
	1	1000	4/6
	2	1000	6/6
Mouse	1	200	0/10
	0.5	500	0/10
	1	500	4/10
	1	1000	6/10
	2	1000	8/10
	4	1000	10/10
Rabbit	1	200	0/10
	2	500	0/4
	4	500	4/4

Endpoint/Concentration/Rationale: NOEL for lethality in mice, rats, and rabbits of 200 ppm for 1 hr

Uncertainty Factors/Rationale:
Total uncertainty factor: 10
Interspecies: 3 - not much variation across species for lethality
Intraspecies: 3 - data support use of 3 (see "Comments")

Modifying Factor: NA

Animal to Human Dosimetric Adjustment: Insufficient data

Time Scaling: $C^n \times t = k$ where n = 3 for extrapolation from longer to shorter durations (10 and 30 min) and n=2 for extrapolation from shorter to longer durations (4 and 8 hr)

Comments: Use of selected value of 10 for intraspecies uncertainty factor and default value of n=3 for extrapolation from shorter to longer time periods results in values that are inconsistent with available toxicity data for allyl alcohol; therefore, values of n = 3 and 2, respectively, were justified